

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/18, 31/63, 47/06, 47/10, 47/32, 9/06, 47/00	A1	(11) International Publication Number: WO 98/37879 (43) International Publication Date: 3 September 1998 (03.09.98)
(21) International Application Number: PCT/EP98/00990 (22) International Filing Date: 20 February 1998 (20.02.98) (30) Priority Data: MI97A000408 25 February 1997 (25.02.97) IT (71) Applicant (for all designated States except US): HELSINN HEALTHCARE S.A. [CH/CH]; Via Pian Scairolo, CH-6912 Pazzallo-Lugano (CH). (72) Inventors; and (75) Inventors/Applicants (for US only): BADER, Stefano [IT/IT]; Via Ponte Vetro, 1, I-20121 Milano (IT). HÄUSERMANN, Enrique [CH/IT]; Via Ponte Vetro, 1, I-20121 Milano (IT). MONTI, Tiziana [IT/CH]; Via Pian Scairolo, CH-6912 Pazzallo-Lugano (CH). (74) Agent: MINOJA, Fabrizio; Bianchetti, Bracco, Minoja S.r.l., Via Rossini, 8, I-20122 Milano (IT).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: NIMESULIDE GEL SYSTEMS FOR TOPICAL USE (57) Abstract The present invention relates to nimesulide topical formulations comprising a carboxyvinylpolymer neutralized as a gel-forming agent or a polyacrylamide-isoparaffin and a solvent selected from the group consisting of ethanol, isopropanol and diethylene glycol monoethyl ether, and to the process for the preparation thereof. Said formulations have advantages such as higher stability of the system and bioavailability of the active ingredient.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

NIMESULIDE GEL SYSTEMS FOR THE TOPICAL USE

The present invention relates to nimesulide topical formulations based on gel systems.

Nimesulide is a known antiinflammatory agent whose therapeutical efficacy has been proved for some time, but which has the drawback of having unfavourable chemical-physical characteristics; the main obstacle to the use of nimesulide in topical formulations is in fact its insolubility in water and, on the other hand, its poor solubility in the solvents/raw materials usually employed in such formulations.

Some formulations of nimesulide for the external use are described in W0 96/11002; said formulations consist in dispersions of particles of the active ingredient throughout a component which, in the case of creams, comprises a hydrophilic polymer, an oily substance, a surfactant agent, a basic substance and water.

The application mentions no gel systems, in particular those in which the active ingredient is dispersed in solvents different from water; moreover the formulations proposed in W0 96/11002 do not solve some problems relating to the stability of the system and to the bioavailability of the active ingredient.

It has now been found that the combination of a gel based on carboxyvinylpolymer or other suitable gel-forming agents with a dispersion of nimesulide in solvents selected from ethanol, isopropanol or diethylene glycol monoethyl ether, gives significant advantages both in terms of stability of the system and

of release and absorption of the active ingredient, therefore improving bioavailability.

The gel-forming action is obtained preferably through neutralization of the carboxyvinylpolymer resin in the acidic form, which chemically behaves as a weak acid; as regards the base to employ in the neutralization, the use of weak bases such as triethanolamine or diisopropanolamine, in a 1:1 acid/base equivalent ratio, turned out to be particularly successful.

The carboxyvinylpolymer used in the gelling process, such as carbomer, is obtained starting from acrylic/methacrylic acid, and it is used in amounts ranging from 0.1% to 5% by weight, preferably 0.5%-2.5%. Alternatively, a polyacrylamide-isoparaffin known under the commercial name Sepigel (Sepic), in amounts ranging from 0.5 to 10% by weight, can be used advantageously as the gel-forming agent.

The use of non aqueous solvents in the preparation of the gel systems of the invention, involves undoubtable advantages both in terms of chemical-physical characteristics and of release and absorption properties of nimesulide. In particular, the invention relates to the use of the solvents ethanol, isopropanol and diethylene glycol monoethyl ether, the latter proving to be particularly effective in increasing the absorption of the active ingredient, thanks to its solvent effect on the lipidic dermal barrier.

Said solvent effect, which although promoting the absorption of nimesulide could affect adversely the dermal hydration, is compensated by the film- and

3

touch- forming properties of the gel based on carboxyvinylpolymer.

Viscosity and pH of the compositions of the present invention can vary within wide ranges: from a few cps to
5 above 100.000 as regards viscosity, whereas the preferred pH range is from 5 to 7. The amount of water can range from 40% to 95% by weight, whereas the amount of solvent, also depending on its contribute to the evaporation of the aqueous phase, is comprised from 5%
10 to 20% by weight for ethanol and isopropanol, preferably about 10%; on the other hand, as far as diethylene glycol monoethyl ether is concerned, the diffusion and permeation properties thereof are related to concentrations from 5% to 40% by weight, preferably
15 about 15%.

The active ingredient nimesulide can be dispersed in a wide range of concentrations, preferably from 0.5% to 7% by weight.

The compositions of the invention can also contain
20 lipophilic excipients, such as caprylic or capric esters, or gliceryl(8)OE, which are capable of improving both the absorption and the final spreadability and "skin-feel" characteristics.

Appropriate preservative systems and lipophilic raw
25 materials suitable for limiting any undesired effects caused by delipidization of the solvent at a superficial level can further be used.

The preservative system provides a microbiological protection by means of wide spectrum antimicrobials,
30 such as imidazolidinyl urea and a balanced parabens mixture; a further guarantee of stability is the

presence of a sequestering agent such as EDTA which is capable of chelating any dangerous ions to keep an appropriate viscosity index.

5 Considering the high percentage of water present, it should be reminded that EDTA warrants an enhancing effect on the preservative system against microorganisms.

The compositions of the invention can further comprise emollients/humectants, such as cetyl esters 1-15% by weight, cholesterol 0.3-0.5% by weight, glycerin 10 1-30% by weight, isopropyl myristate 1-10% by weight, isopropyl palmitate 0.05-5.5% by weight, lecithin 1-20% by weight, lanolin alcohols 0.5-15% by weight, vaseline 4-95% by weight, soy lipids 1-20% by weight, as well as dermal absorption enhancers such as 2-pyrrolidone 0.1-15 10% by weight, propylene glycol 5-50% by weight, pyrrolidone derivatives 0.1-10% by weight.

The compositions of the invention can be prepared according to a process comprising:

- preparation of the dispersed phase containing the 20 carboxyvinylpolymer gel-forming agent;
- addition of the alcoholic solvent, dispersion of the active ingredient nimesulide, addition of preservatives and stabilizing agents;
- neutralization of the resin with the selected base.

25 In the case of systems in which diethylene glycol monoethyl ether is the solvent, the process scheme can be exemplified as follows:

- preparation of the aqueous phase containing the water-soluble preservatives and the 30 carboxyvinylpolymer homogeneously dispersed;
- preparation of the phase containing the

preservatives (parabens) in diethylene glycol monoethyl ether and dispersion of the active ingredient. Addition of the phase consisting of caprylic/capric esters and glyceryl(8)OE;

- 5 - preparation of the dispersion, suspending the phase containing the active ingredient in the aqueous phase containing the carboxyvinylpolymer;
 - preparation of the stabilizers suitably solubilized in the aqueous phase;
 - 10 - neutralization of the resin with the selected base.
- The compositions of the invention have the following advantages:
- capability of solubilizing nimesulide;
 - rapidity and release mechanism of the gel carrier;
 - 15 - capability of promoting absorption;
 - reduction of induced dehydration phenomena.

The compositions of the invention proved to be well tolerated, both in animals (rabbit and guinea pig) and in clinical studies.

- 20 The efficacy of the compositions of the invention has been tested using well-known pharmacological tests, such as the UV-induced erythema in guinea pigs, the croton oil-induced inflammation of the guinea pig ear, the carrageenin-induced granuloma in the rat.

- 25 The dermal adsorption has been studied using ¹⁴C nimesulide both in rats and in human volunteers, no significant systemic concentrations of nimesulide being observed in either of these cases.

- 30 The compositions of the invention were also clinically tested on 200 patients affected with tendinitis of the upper limb or with benign ankle

5

sprains, according to a controlled, double-blind experimental design.

The compositions of the invention turned out to be effective in a statistically significant way, in
5 comparison with placebo.

The following are examples of some preparations obtained with the process of the invention:

EXAMPLE 1

Phase	Ingredient	% w/w
10 Phase A	Purified water	q.s.
	Imidazolidinyl urea	0.20
	EDTA tetrasodium salt	0.10
Phase B	Carbomer (CARBOPOL 1382)	1.20
15 Phase C	Mix parabens	0.20
	Vaseline	1.00
Phase D	Isopropanol	10.00
Phase E	Nimesulide	--
Phase F	Purified water	10.00
20	Triethanolamine	0.60

The formulation was prepared at four nimesulide concentrations, i.e. 2, 3, 4, 5% w/w, each concentration in 3 different 5 kg batches

Phase A + B, i.e. the dispersion of Carbopol in the
25 solution of water and preservatives, was obtained by swelling the gel for two days at room temperature until reaching a homogeneous dispersion. Phase C was prepared in a Gianke & Kunkel Type PM43 paddle mixer heated on a water bath.

30 After the addition of isopropanol, the homogenization was carried out with a Guarniero Mantelli

7

Type F43CV2 homogenizer.

Alternatively, the whole preparation can be performed dispersing Carbopol in water by means of a turbine under vacuum, mixing with paddles after addition of phase C and homogenizing again with the turbine under vacuum after addition of isopropanol.

Paracombin, a powder mixture of methyl, ethyl, propyl, butyl p-hydroxybenzoates, was used as preservative. Methyl, ethyl and propyl p-hydroxybenzoates are cited in Italian Pharmacopoeia XI ed. Butyl p-hydroxybenzoate is cited in USP XXIII.

This mixture was added with the preservative imidazolidinyl urea.

EXAMPLE 2

15		% w/w
	Water	83.40
	Ethanol	10.00
	Nimesulide	3.00
20	Carbomer (CARBOPOL 1382)	1.40
	Petrolatum	1.00
	Triethanolamine	0.70
	Imidazolidinyl urea	0.20
	Methyl, ethyl, propyl parabens	0.20
25	Tetrasodium EDTA	0.10

5	Chemical-physical-characteristics	At preparation	After 45 days at room temp.	After 45 days at temp. = 40°C
	Aspect	Opaque white gel	Opaque white gel	Opaque white gel
10	pH	5.00	5.03	4.98

No traces of separation or decrease in viscosity were observed.

EXAMPLE 3

15		% w/w
	Water	83.40
	Isopropanol	10.00
	Nimesulide	3.00
20	Carbomer (CARBOPOL 1382)	1.40
	Petrolatum	1.00
	Triethanolamine	0.60
	Imidazolidinyl urea	0.20
	Methyl, ethyl, propyl parabens	0.20
25	Tetrasodium EDTA	0.10

5	Chemical- physical- characte- ristics	At prepara- tion	After 45 days at room temp.	After 45 days at temp. = 40°C
	Aspect	Opaque white gel	Opaque white gel	Opaque white gel
10	pH	5.00	5.03	5.01

No traces of separation or decrease in viscosity were observed.

EXAMPLE 4

15	Phase	Ingredient	% w/w
	Phase A	Purified water	q.s.
		Glyceryl (8)OE	
		Caprylate/caprylate	2.00
20		Imidazolidinyl urea	0.20
		EDTA tetrasodium salt	0.10
	Phase B	Carbomer (CARBOPOL 940)	1.00
	Phase C	Mix parabens	0.20
		Diethylene glycol	
25		monoethyl ether	15.00
		Nimesulide	--
	Phase D	Purified water	10.00
		Triethanolamine	0.50

The formulation was prepared at four nimesulide concentrations, i.e. 2%, 3%, 4%, 5% w/w, each concentration in 3 different 5 kg batches.

10
EXAMPLE 5

		% w/w
	Water	83.40
5	Diethylene glycol monoethyl ether	15.00
	Nimesulide	3.00
	Carbomer (CARBOPOL 940)	1.00
	PEG-8 Caprylic/capric glycerids	2.00
	Triethanolamine	0.50
10	Imidazolidinyl urea	0.20
	Methyl, ethyl, propyl parabens	0.20
	Tetrasodium EDTA	0.10

15	Chemical- physical- character- istics	At prepara- tion	After 45 days at room temp.	After 45 days at temp. = 40°C
20	Aspect	Opaque white gel	Opaque white gel	Opaque white gel
	pH	5.20	5.18	5.21

25 No traces of separation or decrease in viscosity
were observed.

CLAIMS

1. Nimesulide topical formulations in the form of gel systems comprising carboxyvinylpolymer neutralized with aqueous solutions of weak bases or a polyacrylamide-isoparaffin and a solvent selected from the group consisting of ethanol, isopropanol, diethylene glycol monoethyl ether.
2. Formulations according to claim 1, in which ethanol and isopropanol are used at a concentration ranging from 5% to 20% by weight.
3. Formulations according to claim 2, in which said concentration is 10% by weight.
4. Formulations according to claim 1, in which the diethylene glycol monoethyl ether is used at a concentration ranging from 5% to 40%.
5. Formulations according to claim 4, in which said concentration is 15%.
6. Formulations according to claims 1-5, in which the weak base used for the neutralization of the carboxyvinylpolymer is triethanolamine or diisopropanolamine.
7. Formulations according to claims 1-6, in which the active ingredient nimesulide is dispersed in a concentration range of 0.5-7% by weight.
8. Formulations according to any of the above claims, further comprising additives selected from emollients, humectants, absorption enhancers, preservatives.
9. Formulations according to claim 8, in which the preservatives are imidazolidinyl urea, parabens and EDTA.

12

10. A process for the preparation of the formulations of claims 1-3 which comprises:

- preparation of the dispersed phase containing the carboxyvinylpolymer gel-forming agent;
- 5 - addition of the alcoholic solvent, dispersion of the active ingredient nimesulide, addition of preservatives and stabilizing agents;
- neutralization of the resin with the selected base.

11. A process for the preparation of the formulations of claims 4-5 which comprises:

- preparation of the aqueous phase containing the water-soluble preservatives and the carboxyvinylpolymer homogeneously dispersed;
- preparation of the phase containing the preservatives (parabens) in diethylene glycol monoethyl ether and dispersion of the active ingredient. Addition of phase consisting of caprylic/capric esters and glyceryl(8)0E;
- 15 - preparation of the dispersion, suspending the phase containing the active ingredient in the aqueous phase containing the carboxyvinylpolymer;
- 20 - preparation of the stabilizers suitably solubilized in the aqueous phase;
- neutralization of the resin with the selected base.

25

INTERNATIONAL SEARCH REPORT

national Application No

PCT/EP 98/00990

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/18 A61K31/63 A61K47/06 A61K47/10 A61K47/32
A61K9/06 A61K47/00

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CHEMICAL ABSTRACTS, vol. 125, no. 4, 22 July 1996 Columbus, Ohio, US; abstract no. 41817, XP002072561 cited in the application see abstract & WO 96 11002 A (HISAMITSU PHARMACEUTICAL CO. INC.,JP) 18 April 1996 ---	1-11
Y,P	EP 0 812 587 A (PANACEA BIOTEC LTD.,IN) 17 December 1997 see claims see example 1 see page 4, line 44 - page 5, line 10 & NZ 299 500 A (PANACEA BIOTEC LTD.,IN) 24 February 1997 --- -/--	1-11

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

24 July 1998

Date of mailing of the international search report

05/08/1998

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Scarponi, U

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 98/00990

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y,P	WO 98 01124 A (ERREKAPPA EUROTERRAPICI S.P.A.,MI (IT)) 15 January 1998 see examples 1,2 ---	1-11
Y,P	US 5 716 609 A (R.JAIN ET AL.) 10 February 1998 see claims see example 1 ---	1-11
Y,P	DATABASE WPI Week 9720 Derwent Publications Ltd., London, GB; AN 97-225967 '20! XP002072562 see abstract & WO 97 12608 A (HELSINN HEALTHCARE SA) 10 April 1997 ---	1-11
A	EP 0 532 900 A (LPB ISTITUTO FARMACEUTICO S.P.A.,MI (IT)) 24 March 1993 see the whole document -----	1-11

INTERNATIONAL SEARCH REPORT

Information on patent family members

II. National Application No

PCT/EP 98/00990

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 812587	A	17-12-1997	NZ 299500 A	24-02-1997
WO 9801124	A	15-01-1998	IT RM960480 A	05-01-1998
			EP 0853476 A	22-07-1998
US 5716609	A	10-02-1998	EP 0812591 A	17-12-1997
			NZ 299481 A	22-09-1997
			US 5688829 A	18-11-1997
			HU 9601442 A	28-04-1998
EP 532900	A	24-03-1993	IT 1251838 B	26-05-1995
			JP 5213743 A	24-08-1993
			US 5283261 A	01-02-1994